

REMARKS

Please reconsider the application in view of the above amendments and the following remarks. Applicant thanks the Examiner for carefully considering this application.

Disposition of Claims

Claim 16 has been canceled. Therefore, claims 1-15, 17-27, and 29-32 are currently under consideration. Claim 1 is independent. Remaining claims depend, directly or indirectly, from claim 1.

Claim Amendments

Claim 1 has been amended by incorporation of the limitation recited in original claim 16. As a result, claim 16 has been canceled. Claim 20 has been amended to correct the term "TGF-beta." Claims 6, 13, 19, and 21-24 have been amended to clarify the invention. No new matter is introduced by these amendments.

Claim Rejections under 35 U.S.C. § 103

Claims 1-10, 12-14, 16-19, 25, 26, and 29-32

Claims 1-10, 12-14, 16-19, 25, 26, and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brocchini et al. (U.S. 2002/0082362) (hereinafter "Brocchini") as applied to claim 1 above, in further view of Neuenschwander et al. (U.S. 5,665,831) (hereinafter "Neuenschwander"). Claim 1 has been amended. To the extent

that this rejection may still apply to the amended claims, this rejection is respectfully traversed.

Applicant respectfully submits that the amended claims are not obvious at least because the prior art Brocchini and Neunschwander references in fact teach one of ordinary skill in the pertinent art at the time of the claimed invention against combining them, because one so skilled at the time of this invention would have expected a combination of the references would not produce operative subject matter such as that of the claimed invention. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be shown or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ (C.C.P.A., 1074).

Under the current law of obviousness, including under the Supreme Court's *KSR* decision, an obviousness rejection cannot be based on a combination of references to show the claimed subject matter where the references sought to be combined teach one of ordinary skill in the art away from combining them. This was reiterated by the Supreme Court in *KSR* as follows:

In *United States v. Adams*, 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966), a companion case to *Graham*, the Court considered the obviousness of a "wet battery" that varied from prior designs in two ways: It contained water, rather than the acids conventionally employed in storage batteries; and its

electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. 383 U.S., at 50-51, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293. It nevertheless rejected the Government's claim that Adams' battery was obvious. The Court relied upon the corollary principle that *when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. Id.*, at 51-52, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293. When Adams designed his battery, *the prior art warned that risks were involved in using the types of electrodes he employed. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams' design was not obvious to those skilled in the art.*

KSR Int'l v. Teleflex, Inc., 550 U.S. 398, 416 (2007) (emphasis added). As further held by US courts: "Rather than being made obvious by the reference, such modification would run counter to its teaching by rendering the apparatus inoperative." In re Schulpen, 157 USPQ 52 (CCPA 1968).

Here, the obviousness rejection is based on an asserted combination of prior art references that, in fact, teach one of ordinary skill in the art at the time of the invention against and ways from making the asserted combination. It is exactly this type of alleged “obvious combination” that is, and always has been, impermissible under Section 103, obviousness.

Brocchini teaches bioactive molecules conjugated with soluble polyacetal polymers. The soluble polyacetal polymers are relatively stable at physiological pH but degrade readily in low pH conditions. (Abstract). In particular, Brocchini’s polyacetal polymers are physiologically soluble in water and water solutions, such as saline, phosphate buffered saline (PBS), and other buffered solutions. (¶ [0108]). Brocchini teaches that the soluble polyacetal polymers may degrade during cellular uptake due to an increase in acidity within the lysosomes during endocytosis, in acidic regions of the gastrointestinal tracts, and at sites of diseased tissues, such as solid tumors, thus, releasing the conjugated bioactive molecules. (¶¶ [0011] and [0122]). For example, comparing 1h (1) with 505 h (6), at 37°C, polyacetal 3 degrades at a faster rate at pH 5.5 (which is within the range of lysosomal pH) (FIG. 2), than that at pH 7 (FIG. 1). (¶¶ [0120] and [0122]). Likewise, at 37°C, polyacetal polymer 22 degrades at a faster rate at pH 5.5 than that at pH 7.4. (¶ [0122] and FIG. 7). Therefore, a skilled artisan would know that Brocchini’s polyacetal polymers are soluble and/or in liquid phase at 37°C in physiological solutions, regardless of the pH.

Neunschwander teaches block copolymers suitable for the production of medical implants and surgical aids. (Abstract). One important property of

Neunschwander's block copolymers is their thermoplastic processability. Neunschwander teaches that the block copolymers can be melt processed at temperatures between 80°C and 200°C, thus, providing the advantage of adaptability of the shape and size of the medical implants and surgical suture materials, prior to use. (Col. 9, lines 45-53; and claim 17). In other words, the melting temperature of Neunschwander's block copolymers is between 80°C and 200°C. It was well known in the art at the time of the claimed invention that at the melting point of a polymer the solid phase and the liquid phase of the material exist in equilibrium. Therefore, a skilled artisan would know that at human body temperature, 37°C, Neunschwander's block copolymers would be solid because 37°C is well below the melting point of Neunschwander's block copolymers (melting point between 80°C and 200°C).

Indeed, Neunschwander's block copolymers must be solid at and near human body temperature (at and near 37°C) because Neunschwander's block copolymers are used as solid, implanted medical devices.

As a result, common sense would not have led one skilled in the art to substitute Brocchini's polyacetal polymers, which are clearly required to be soluble at 37°C in physiological conditions, with Neunschwander's block copolymers, which are clearly required to be solid at 37°C. Even now, it is clear to one of ordinary skill in the art that such a substitution would necessarily render Brocchini's polyacetal soluble drug delivery polymers inoperative, and vice versa, in rendering Neunschwander's solid medical devices inoperative. Therefore, Brocchini and Neunschwander teach one away from combining them, as one of ordinary skill in the art at the time of the invention

would have expected any such combination of the references to produce operative subject matter, including the claimed subject matter.

Further, the present invention relates to biodegradable polymers having high mechanical strength and their use for the manufacture of load bearing medical devices suitable for implantation within the body. (¶ [0001]). To achieve high mechanical strength, embodiments of the present invention include copolymers having strength blocks, which serve as the main strength components of the polymer. (¶ [0039]). One of the characteristics of the polymers of the present invention is crystallinity. (¶ [0042]). The inclusion of these high strength crystalline polymers increases the melt transition temperatures (T_m) of the copolymers above the normal body temperature of 37°C.

Embodiments of the present invention include injecting biodegradable segmented block polymers into a patient's body where they conform to the dimensions of a desired location in the body then cool and harden *in situ* to a desired solid form. In these embodiments, the polymers are temporarily heated above 37°C, *ex vivo* and prior to injection, so that they are sufficiently pliable to be injected and set in place to harden *in situ* at normal body temperature of about 37°C. (¶ [0032]). To achieve both high strength and injectability *in situ* of block polymers, the polyol residues of the present invention may have a low melting point, e.g., from about 50°C to about 80°C, and may include polyesters having a low melting point (I., "low melting point polyesters" as discussed in the specification), such as polycaprolactone or polybutyladipate. (¶ [0033]).

For example, the T_m of polycaprolactone diols (PCL) with various block size ranges from 40.5°C to 67.3°C (Table 1c); and the T_m of polyacetal (PCL/CHDM/CHDMDVE) compositions ranges from 46.4°C to 54°C (Table 3c). As a result, the medical devices made from the high mechanical strength and low melting point copolymers of the present invention would allow the materials to be formed/shaped/set *in situ* and to be used in the body. (¶ [0034]). However, it remains imperative that the compositions of the claimed invention must be solid (*i.e.*, well below their melt point) at and near body temperature (37°C).

Therefore, claim 1 requires, *inter alia*, “wherein the polyol residues have a melting point between about 50°C and 80°C.”

Brocchini teaches soluble, degradable polyacetal polymers for use in pharmaceutical and biomedical applications. (Abstract; and ¶¶ [0005]-[0007], [0108], and [0122]). Specifically, Brocchini teaches that polymers are and must be hydrophilic or water-soluble at 37°C for ease of delivery of drugs and the like to animals and patients for treatment. (¶¶ [0108] and [0122]; and FIG. 7). Because Brocchini’s polyacetal polymers are soluble or in liquid phase at 37°C, a skilled artisan would know that the melting temperature of Brocchini’s polyacetal polymers would be at or below 37°C. As a result, Brocchini does not teach or suggest to one of ordinary skill in the art, now or at the time of this invention, “wherein the polyol residues have a melting point between about 50°C and 80°C,” as required by claim 1.

Neuenschwander teaches biocompatible multi-block copolymers containing α,ω -dihydroxypolyesters and α,ω -dihydroxypolyethers. (Abstract). Specifically, Neuenschwander teaches that the copolymers have a melting temperature of 80°C-200°C. (Col. 9, lines, 45-49; and claim 17). In other words, Neuenschwander's copolymers do not have a low melting point from about 50°C to about 80°C. (§ [0033]). Therefore, Neuenschwander does not teach or suggest what is missing in Brocchini, *i.e.*, "wherein the polyol residues have a melting point between about 50°C and 80°C."

As noted above, even assuming *arguendo* that Neuenschwander was combinable with Brocchini, common sense would not have led a skilled artisan to substitute Brocchini's polymers, which are soluble at 37°C, with Neuenschwander's copolymers, which are solid at 37°C, in physiological solutions. Such a combination would necessarily make the asserted bioactive molecules of both conjugated with copolymers insoluble at 37°C in physiological conditions, thus, defeating entirely the purpose of Brocchini's polymers, which are to deliver soluble bioactive molecules to animals and/or patients in vivo at 37°C. In other words, such an asserted combination would render Brocchini's polymers inoperative.

In the same manner, one skilled in the art would not substitute Neuenschwander's copolymers, which are solid at 37°C, with Brocchini's polymers, which are soluble at 37°C, in physiological solutions, because such a combination would render Neuenschwander's copolymers entirely inoperative as solid medical implant materials.

As a result, Brocchini and Neuenschwander, considered separately or in combination, fail to teach or suggest all the limitations recited in claim 1. Therefore, claim 1 is patentable over Brocchini in view of Neuenschwander. Claim 16 has been canceled. Dependent claims 2-10, 12-14, 17-19, 25, 26, and 29-32 should also be patentable for at least the same reasons, as the combination of the cited Brocchini and Neuenschwander art for alleged obviousness does not render obvious the subject matter of claim 1, and each of these claims depend directly or indirectly from claim 1. Thus, if anything, these claims are even less obvious than claim 1 was asserted to be over the cited art. Accordingly, withdrawal of these obviousness rejections is respectfully requested.

Claim 11

Claims 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brocchini in view of Neuenschwander as applied to claim 1 above, in further view of Shalaby (U.S. 6,503,991) (hereinafter "Shalaby"). Claim 1 has been amended. To the extent that this rejection may still apply to the amended claims, this rejection is respectfully traversed.

As noted above, claim 1 is patentable over Brocchini in view of Neuenschwander.

Shalaby teaches crystalline, absorbable block/segmented copolymers. (Abstract). However, these copolymers must be incapable of crystallization between 25-

50°C. (Col. 3, lines 12-13). In other words, the melting temperature of Shalaby's copolymers must be at or below 25°C - 50°C. Thus, Shalaby does not teach or suggest what is **missing** in Brocchini and Neuenschwander, *i.e.*, "wherein the polyol residues have a melting point between about 50°C and 80°C," as would be required for the art to render claim 1 obvious. The lack of Shalaby disclosing anything of relevance to claim 1 is evident by the fact that the Examiner relies on Shalaby solely to teach the "carbonate" of claim 11. (Final Office Action, p. 5, line 7).

As a result, Brocchini, Neuenschwander, and Shalaby, considered separately or in combination, fail to teach or suggest all the limitations recited in claim 1. Therefore, claim 1 is patentable over Brocchini in view of Neuenschwander and further in view of Shalaby. Dependent claim 11 is therefore also patentable for at least the same reasons. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 15, 25, and 27

Claims 15, 25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brocchini in view of Neuenschwander as applied to claims 1 and 14 above, in further view of Wise et al. (U.S. 6,071,982) (hereinafter "Wise"). Claim 1 has been amended. To the extent that this rejection may still apply to the amended claims, this rejection is respectfully traversed.

As noted above, claim 1 is patentable over Brocchini in view of Neuenschwander.

Wise teaches bioerodible polymeric semi-IPN alloys. (Abstract). However, Wise does not teach or suggest what is missing in Brocchini and Neuenschwander, i.e., “wherein the polyol residues have a melting point between about 50°C and 80°C,” as would be required to render claim 1 obvious. The lack of relevance of Wise to claim 1 is evident by the fact that the Examiner relies on Wise only to teach the “buffer” of dependent claims 15, 25, and 27, and not to reject claim 1. (Final Office Action, p. 6, line 4).

As a result, Brocchini, Neuenschwander, and Wise, considered separately or in combination, fail to teach or suggest all the limitations recited in claim 1. Therefore, claim 1 is patentable over Brocchini in view of Neuenschwander and further in view of Wise. Because dependent claims 15, 25, and 27 cannot be obvious without at least claim 1 being obvious, claims 15, 25, and 27 are patentable over the cited art. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 20 and 22

Claims 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brocchini in view of Neuenschwander as applied to claim 19 above, in further view of Pathak et al. (U.S. 6,923,986) (hereinafter “Pathak”). Claim 1 has been amended. To the extent that this rejection may still apply to the amended claims, this rejection is respectfully traversed.

As noted above, claim 1 is patentable over Brocchini in view of Neuenschwander.

Pathak teaches gel-forming macromers. (Abstract). However, Pathak does not teach or suggest what is missing in Brocchini and Neuenschwander, i.e., “wherein the polyol residues have a melting point between about 50°C and 80°C,” as is required to render claim 1 obvious. The lack of relevance of Pathak to claim 1 is evident by the fact that the Examiner relies on Pathak solely to teach the “growth factors or growth agents” of claims 20 and 22 (Final Office Action, p. 7, line 1).

As a result, Brocchini, Neuenschwander, and Pathak, considered separately or in combination, fail to teach or suggest all the limitations recited in claim 1. Therefore, claim 1 is patentable over Brocchini in view of Neuenschwander and further in view of Pathak. Dependent claims 20, and 22 are, therefore, also not obvious over the cited art at least because claim 1, from which they depend, is not obvious. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 21

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brocchini in view of Neuenschwander as applied to claim 19 above, in further view of Tormala (U.S. 6,579,533) (hereinafter “Tormala”). Claim 1 has been amended. To the

extent that this rejection may still apply to the amended claims, this rejection is respectfully traversed.

As noted above, claim 1 is patentable over Brocchini in view of Neuenschwander.

Tormala teaches synthetic bioabsorbable drug delivery materials and implants. (Abstract). However, Tormala does not teach or suggest what is missing in Brocchini and Neuenschwander, i.e., “wherein the polyol residues have a melting point between about 50°C and 80°C,” as is required by claim 1. The lack of relevance of Tormala to claim 1 is evident by the fact that the Examiner relies on Tormala solely to teach the “antibiotic” of claim 21, and does not apply Tormala to claim 1. (Final Office Action, p. 7, line 20).

As a result, Brocchini, Neuenschwander, and Tormala, considered separately or in combination, fail to teach or suggest all the limitations recited in claim 1. Therefore, claim 1 is patentable over Brocchini in view of Neuenschwander and further in view of Tormala. Because claim 21 depends from claim 1, it is not obvious at least because of the reasons that claim 1 is not obvious over the cited art. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 23

Claims 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brocchini in view of Neuenschwander as applied to claim 19 above, in further view of Uhrich (U.S. 2002/0071822) (hereinafter "Uhrich"). Claim 1 has been amended. To the extent that this rejection may still apply to the amended claims, this rejection is respectfully traversed.

As noted above, claim 1 is patentable over Brocchini in view of Neuenschwander.

Uhrich teaches polymers which degrade hydrolytically into biologically active compounds. (Abstract). However, Uhrich does not teach or suggest what is missing in Brocchini and Neuenschwander, i.e., "wherein the polyol residues have a melting point between about 50°C and 80°C," as is required to render obvious the subject matter of claim 1. The lack of relevance of Uhrich to claim 1 is evident by the fact that the Examiner relies on Uhrich only to teach the "methotrexate" of claim 23. (Final Office Action, p. 8, line 14).

As a result, Brocchini, Neuenschwander, and Uhrich, considered separately or in combination, fail to teach or suggest all the limitations recited in claim 1. Therefore, claim 1 is patentable over Brocchini in view of Neuenschwander and further in view of Uhrich. Because dependent claim 23 depends from claim 1, and claim 1 is not obvious over the cited art, claim 23 cannot be obvious over the cited art which would

have to render obvious the combination of the subject matter of claims 1 and 23. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 24

Claims 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brocchini in view of Neuenschwander as applied to claim 19 above, in further view of Heller (U.S. 7,045,589) (hereinafter “Heller”). Claim 1 has been amended. To the extent that this rejection may still apply to the amended claims, this rejection is respectfully traversed.

As noted above, claim 1 is patentable over Brocchini in view of Neuenschwander.

Heller teaches bioerodible poly(ortho esters) useful as orthopedic implants or vehicles for the sustained delivery of pharmaceutical, cosmetic and agricultural agents. (Abstract). Specifically, Heller teaches that poly(ortho esters) has a very high viscosity at normal body temperature of 37°C. (Col. 25, lines 60-62). In other words, Heller’s polymers have a melting temperature at least at or below 37°C. Therefore, Heller does not teach or suggest what is missing in Brocchini and Neuenschwander, i.e., “wherein the polyol residues have a melting point between about 50°C and 80°C,” as is required to render obvious claim 1. The lack of relevance of Heller to claim 1 is evident by the fact that the Examiner relies on Heller only to teach the “pain killer” of claim 24. (Final Office Action, p. 9, line 10).

As a result, Brocchini, Neuenschwander, and Heller, considered separately or in combination, fail to teach or suggest all the limitations recited in claim 1. Therefore, claim 1 is patentable over Brocchini in view of Neuenschwander and further in view of Heller. Dependent claim 24 depends from claim 1 and therefore includes all the subject matter of claim 1 and the additional subject matter of claim 24. Because the Examiner has failed to make a prima facie case of obviousness of claim 1, claim 24 cannot be obvious either over the cited prior art because not even the base subject matter is obvious. Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

Applicant believes the application is in condition for allowance. If this belief is incorrect, or other issues arise, the Examiner is encouraged to contact the undersigned at the telephone number listed below.

Should the Examiner believe that there are remaining issues to be resolved in this application that cannot be resolved over the telephone with Applicant's undersigned attorney, Applicant respectfully requests that the Examiner issue an Advisory Action as soon as possible. This will allow Applicant as much time as possible to review the Advisory Action and to properly address any remaining issues in an appropriate post-Final filing with the US Patent Office, which must be made no later than March 16, 2011.

Please apply any charges not covered, or any credits, to Deposit Account
50-0591 (Reference Number 17771/004001).

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